nature medicine

SUPPLEMENTARY INFORMATION

https://doi.org/10.1038/s41591-018-0053-3

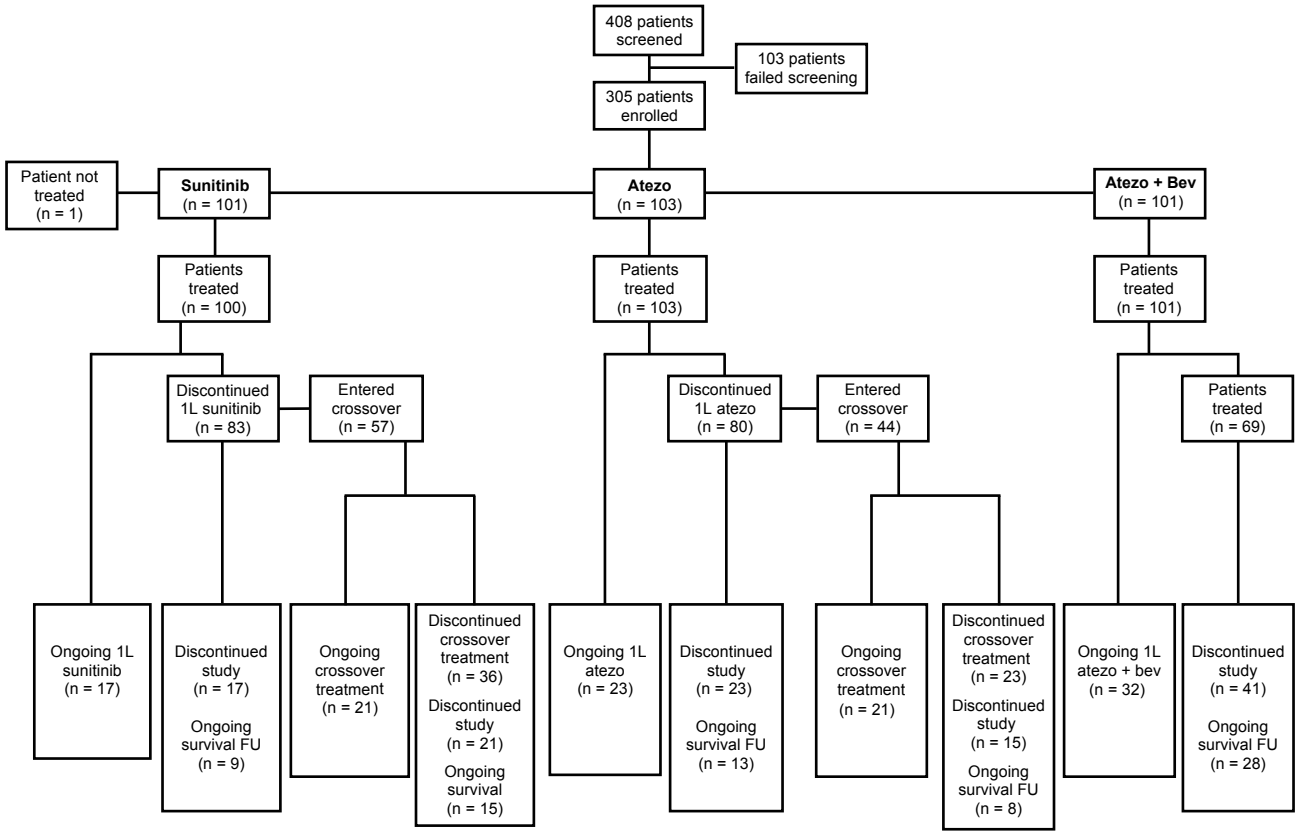
In the format provided by the authors and unedited.

Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma

David F. McDermott[1]*, Mahrukh A. Huseni[2], Michael B. Atkins[3], Robert J. Motzer[4], Brian I. Rini[5], Bernard Escudier[6], Lawrence Fong[7], Richard W. Joseph[8], Sumanta K. Pal[9], James A. Reeves[10], Mario Sznol[11], John Hainsworth[12], W. Kimryn Rathmell[13], Walter M. Stadler[14], Thomas Hutson[15], Martin E. Gore[16], Alain Ravaud[17], Sergio Bracarda[18], Cristina Suárez[19], Riccardo Danielli[20], Viktor Gruenwald[21], Toni K. Choueiri[22], Dorothee Nickles[2], Suchit Jhunjhunwala[2], Elisabeth Piault-Louis[2], Alpa Thobhani[23], Jiaheng Qiu[2], Daniel S. Chen[2], Priti S. Hegde[2], Christina Schiff[2], Gregg D. Fine[2] and Thomas Powles[24]

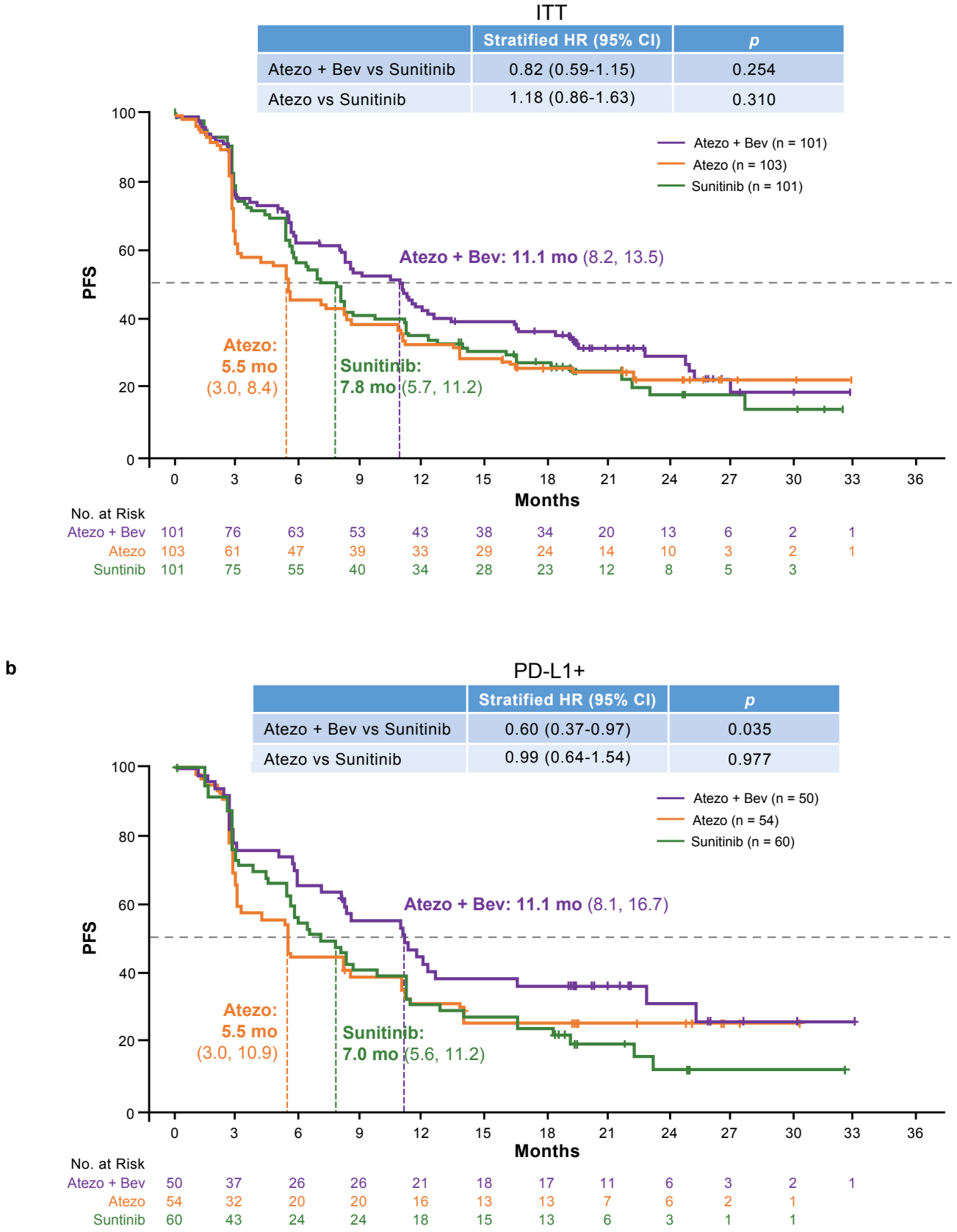
[1]Beth Israel Deaconess Medical Center, Boston, MA, USA. [2]Genentech, Inc., South San Francisco, CA, USA. [3]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA. [4]Memorial Sloan Kettering Cancer Center, New York, NY, USA. [5]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA. [6]Gustave Roussy, Villejuif, France. [7]University of California, San Francisco School of Medicine, San Francisco, CA, USA. [8]Mayo Clinic Hospital – Florida, Jacksonville, FL, USA. [9]City of Hope Comprehensive Cancer Center, Duarte, CA, USA. [10]Florida Cancer Specialists, Fort Myers, FL, USA. [11]Yale School of Medicine, New Haven, CT, USA. [12]Sarah Cannon Research Institute, Nashville, TN, USA. [13]Vanderbilt University Medical Center, Nashville, TN, USA. [14]University of Chicago Medicine, Chicago, IL, USA. [15]Texas Oncology – Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA. [16]Royal Marsden Hospital, London, UK. [17]CHU Hopitaux de Bordeaux – Hôpital Saint-André, Bordeaux, France. [18]Ospedale San Donato, Azienda USL Toscana Sudest, Arezzo, Italy. [19]Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain. [20]Azienda Ospedaliera Universitaria Senese, Center for Immune-Oncology, Siena, Italy. [21]Medizinische Hochschule, Zentrum Innere Medizin, Abt. Hämatologie u. Onkologie, Hannover, Germany. [22]Dana-Farber Cancer Institute, Boston, MA, USA. [23]Roche Products Ltd, Welwyn Garden City, UK. [24]Barts Cancer Institute and the Royal Free Hospital, Queen Mary University of London, London, UK. *e-mail: dmcdermo@bidmc.harvard.edu

Supplementary Figure 1



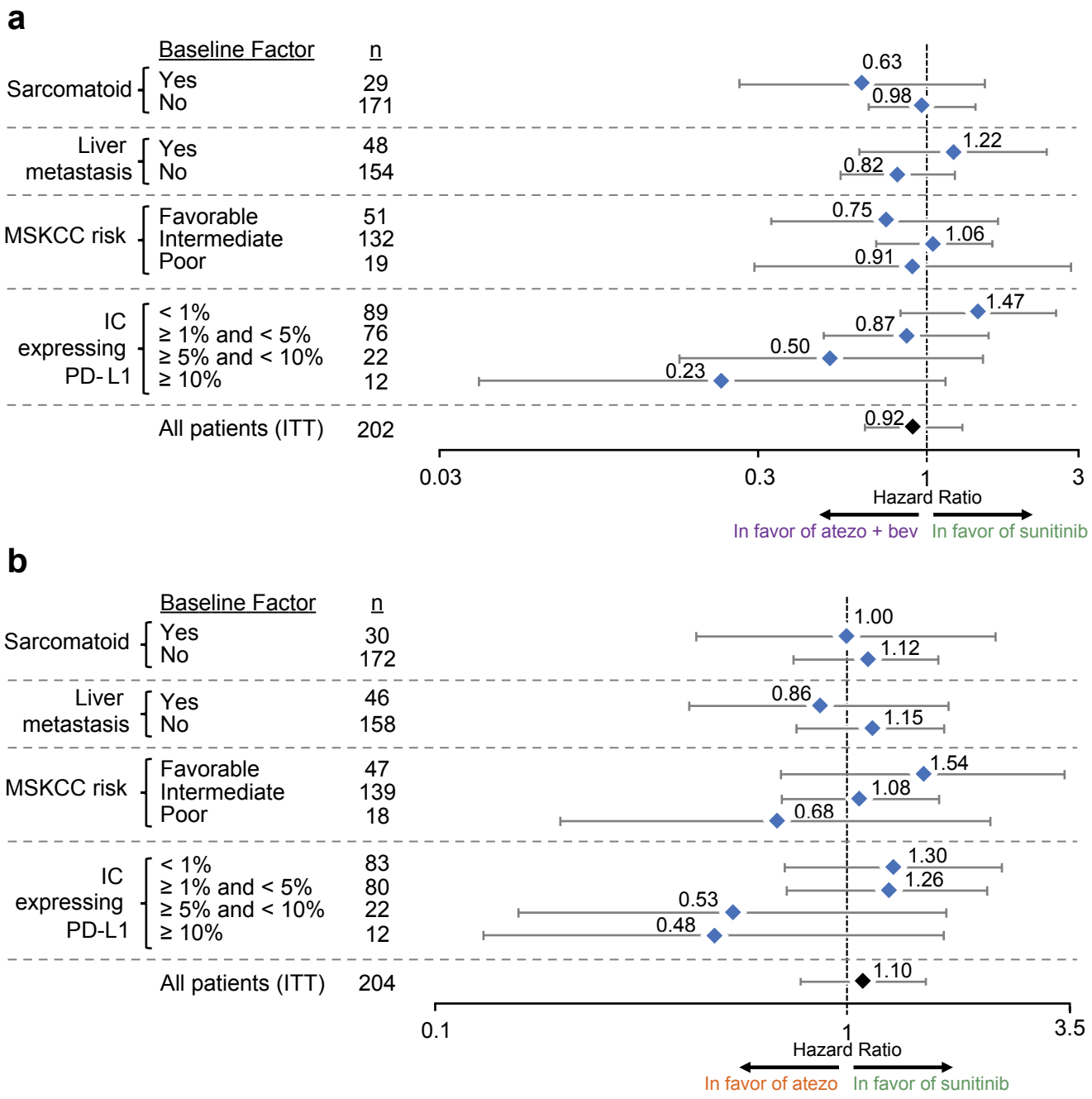
IMmotion150 trial profile. Flowchart of patients randomized to 1 of 3 treatment arms: sunitinib, atezolizumab (atezo) monotherapy, or atezo + bevacizumab (bev) in combination. One patient in the sunitinib arm did not receive study drug due to withdrawal of consent and was excluded from the safety analysis. 1L, first line; FU, follow-up.

Supplementary Figure 2



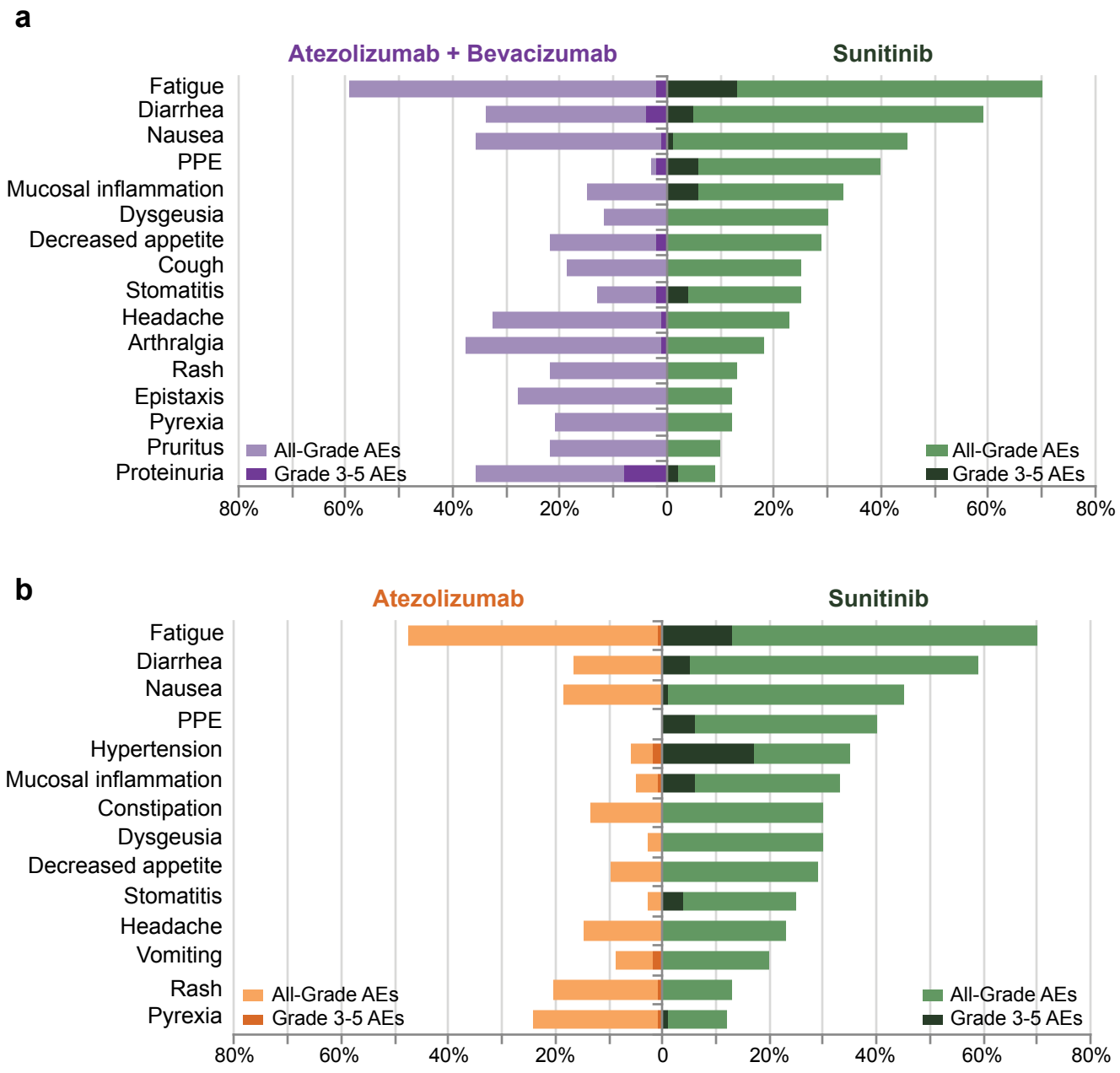
Investigator-assessed PFS associated with atezolizumab + bevacizumab in patients with metastatic renal cell carcinoma with PD-L1+ IC. Kaplan-Meier curves depict investigator-assessed median progression-free survival (PFS) in the atezolizumab (atezo) + bevacizumab (bev), atezo monotherapy, and sunitinib treatment arms in the (**a**) intent-to-treat (ITT) population and (**b**) programmed death-ligand 1–positive (PD-L1+; ≥ 1% PD-L1 expression on tumor-infiltrating immune cells [IC] by immunohistochemistry) population across 33 months. Censored data are indicated by vertical tick marks in Kaplan-Meier curves. Sample number (No.) per group and time point are indicated below the graphs. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using stratified Cox proportional hazards regression models, and *p* values were calculated using stratified log-rank test (for details, see Methods section). All *p* values are provided for descriptive purposes only and were not adjusted for multiple comparisons.

Supplementary Figure 3



Independent review facility–assessed PFS in key subgroups. Forest plots depicting median progression-free survival (PFS) vs sunitinib in specific patient subgroups for (**a**) atezolizumab (atezo) + bevacizumab (bev) and (**b**) atezo monotherapy. The analyses were unstratified. Sample number (n) per group is indicated on graph. Center values (blue diamond) denote median PFS and error bars refer to 95% confidence intervals. IC, tumor-infiltrating immune cells; ITT, intent-to-treat; MSKCC, Memorial Sloan Kettering Cancer Center; PD-L1, programmed death-ligand 1.

Supplementary Figure 4



Supplementary Figure 4

c

Selected AEs of special interest

n (%)	Sunitinib n = 100	Atezo + Bev n = 101	Atezo n = 103	Sunitinib n = 100	Atezo + Bev n = 101	Atezo n = 103
	All Grade			Grade 3/4		
Pneumonitis	0	0	1 (1%)	0	0	0
Colitis	1 (1%)	1 (1%)	0	0	0	0
Elevated liver enzymes/hepatitis	20 (20%)	16 (16%)	9 (9%)	4 (4%)	4 (4%)	3 (3%)
TSH decreased/ hypothyroidism	20 (20%)	23 (23%)	15 (15%)	0	0	0
TSH increased/ hyperthyroidism	6 (6%)	7 (7%)	5 (5%)	0	0	0
Decreased blood cortisol/adrenal insufficiency	0	3 (3%)	0	0	1 (1%)	0

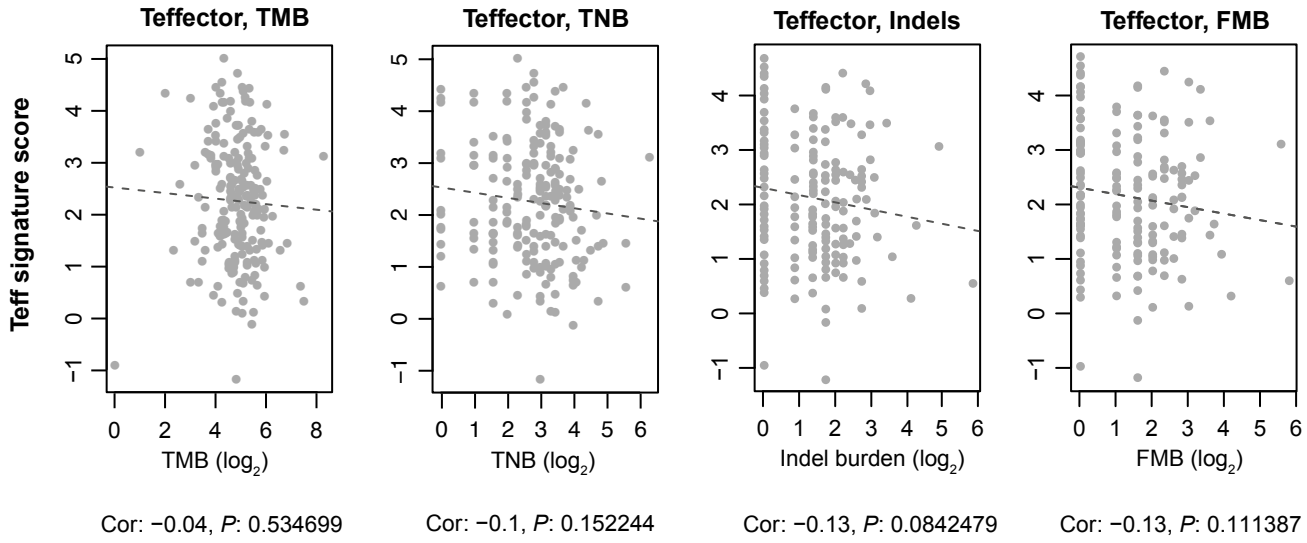
d

All AEs occurring in ≥ 20% of patients in any arm

n (%)	Sunitinib (n = 100)	Atezo (n = 103)	Atezo + Bev (n = 101)
Any AE	**99 (99.0%)**	**101 (98.1%)**	**101 (100.0%)**
Fatigue	70 (70.0%)	49 (47.6%)	60 (59.4%)
Arthralgia	18 (18.0%)	15 (14.6%)	38 (37.6%)
Hypertension	35 (35.0%)	6 (5.8%)	37 (36.6%)
Proteinuria	9 (9.0%)	8 (7.8%)	36 (35.6%)
Diarrhea	59 (59.0%)	17 (16.5%)	34 (33.7%)
Nausea	45 (45.0%)	19 (18.4%)	36 (35.6%)
Headache	23 (23.0%)	15 (14.6%)	33 (32.7%)
Constipation	30 (30.0%)	14 (13.6%)	28 (27.7%)
Epistaxis	12 (12.0%)	2 (1.9%)	28 (27.7%)
Rash	13 (13.0%)	21 (20.4%)	22 (21.8%)
Pruritus	10 (10.0%)	16 (15.5%)	22 (21.8%)
Decreased appetite	29 (29.0%)	10 (9.7%)	22 (21.8%)
Pyrexia	12 (12.0%)	25 (24.3%)	21 (20.8%)
Vomiting	20 (20.0%)	9 (8.7%)	19 (18.8%)
Cough	25 (25.0%)	23 (22.3%)	19 (18.8%)
Mucosal inflammation	33 (33.0%)	4 (3.9%)	15 (14.9%)
Stomatitis	25 (25.0%)	3 (2.9%)	13 (12.9%)
Dysgeusia	30 (30.0%)	3 (2.9%)	12 (11.9%)
PPE	40 (40.0%)	–	3 (3.0%)
Infections and infestations	32 (32.0%)	42 (40.8%)	63 (62.4%)

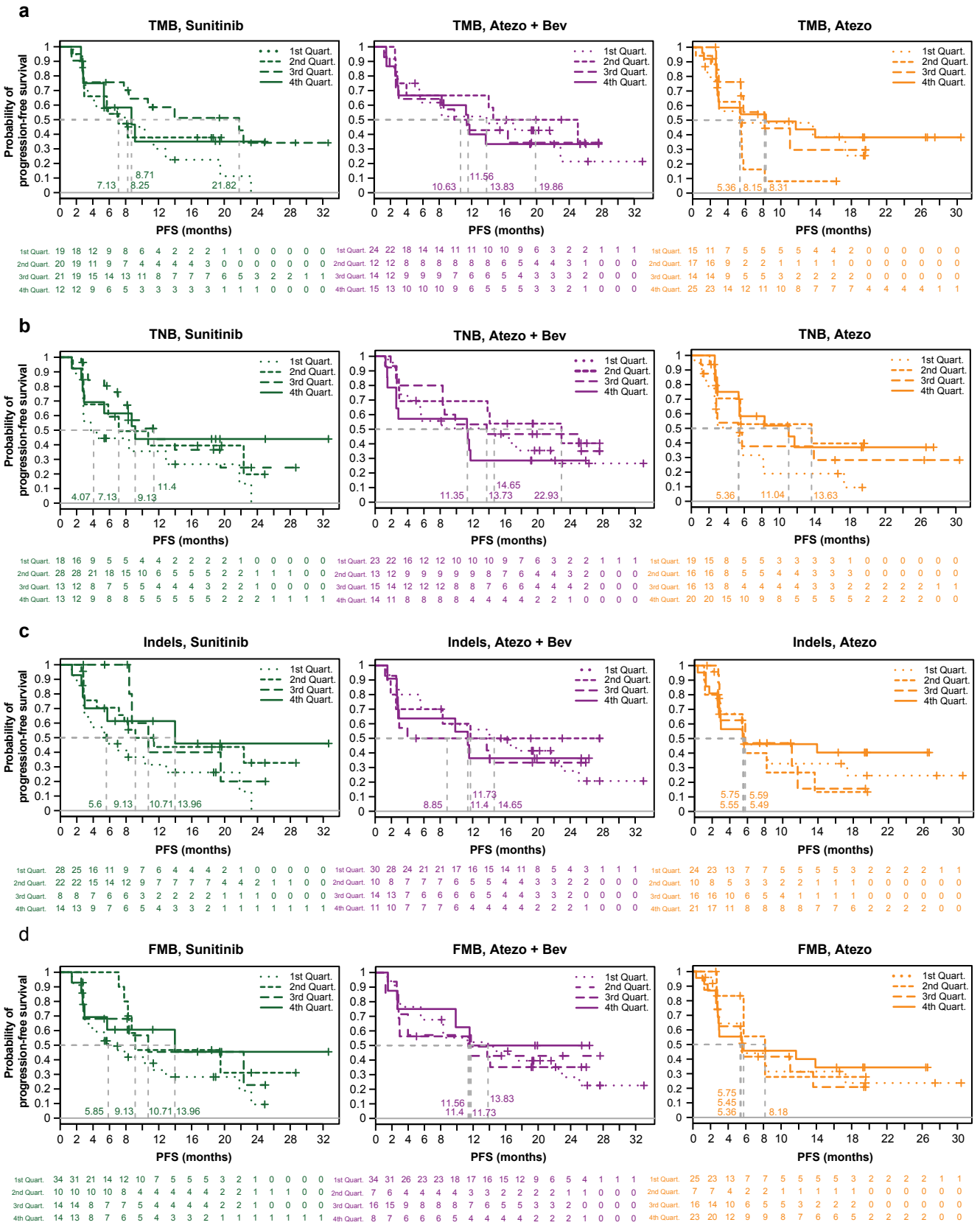
All-cause adverse events in the safety population. Adverse events (AEs) with > 5% difference between and a ≥ 20% frequency in either arm are shown in the (**a**) atezolizumab + bevacizumab vs sunitinib and (**b**) atezolizumab vs sunitinib populations. Patient numbers (n) per AE are reported in panel d. (**c**) Selected AEs of special interest. (**d**) All AEs occurring in ≥ 20% of patients in any arm. Atezo, atezolizumab; Bev, bevacizumab; PPE, palmar-plantar erythrodysesthesia; TSH, thyroid-stimulating hormone.

Supplementary Figure 5



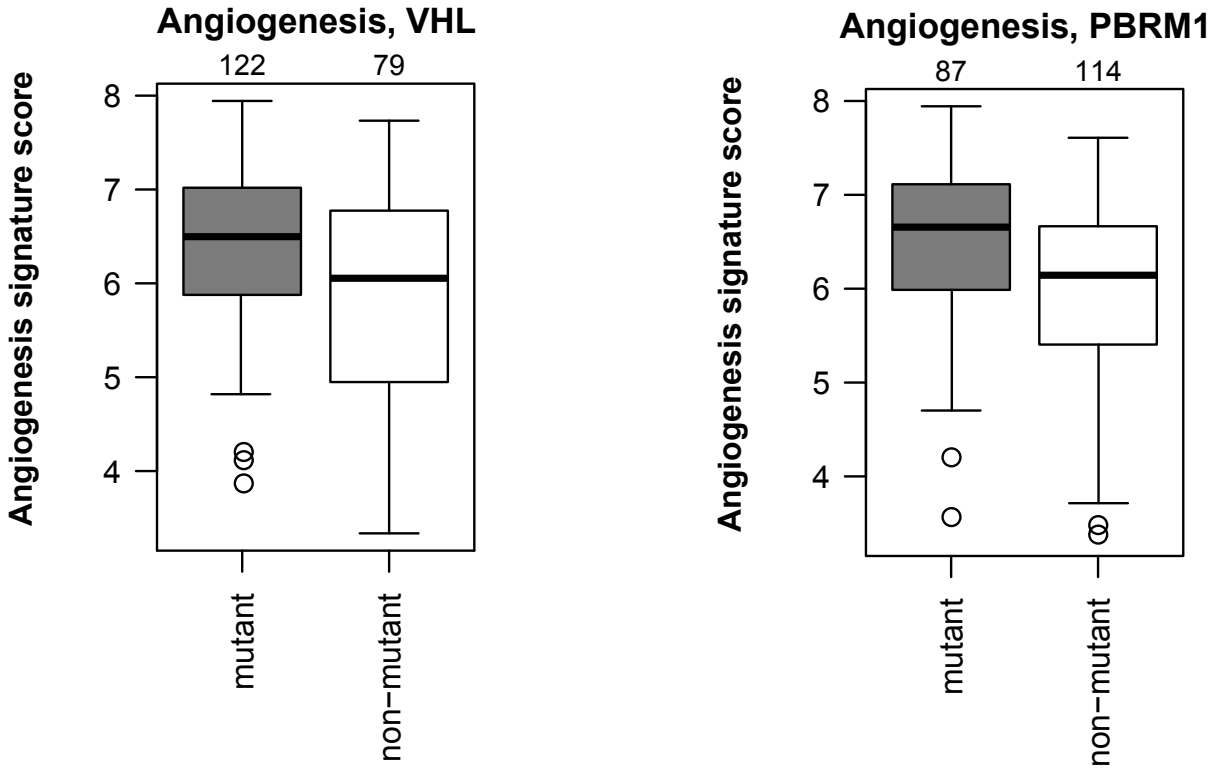
Correlation between TMB, TNB, indel burden, or FMB and Teff signature scores. Tumor mutation burden (TMB), tumor neoantigen burden (TNB), indel burden, and frameshift mutation burden (FMB) (x-axes) were $\log_2$ transformed before Pearson correlations (Cor) with Teffector (Teff) signature scores (y-axes) and corresponding *p* values (two-sided test) were computed. Analyses based on n = 201 (TMB), n = 193 (TNB), n = 169 (indel) and n = 160 (FMB) samples.

Supplementary Figure 6



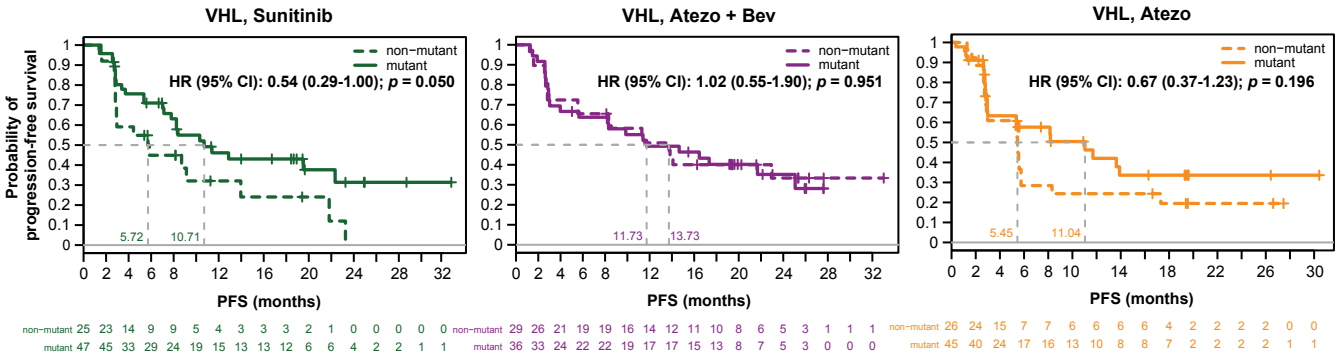
Association between TMB, TNB, indel burden, or FMB and PFS in the three treatment arms. Kaplan-Meier plots compare patient groups created on the basis of (**a**) tumor mutation burden (TMB), (**b**) tumor neoantigen burden (TNB), (**c**) indels, or (**d**) frameshift mutation burden (FMB) quartiles (Quart) in each of the three treatment arms. There is no evidence of progression-free survival (PFS) associated with different quartiles of TMB, TNB, indels, or FMB in the sunitinib (likelihood ratio test, $p = 0.306$, $p = 0.237$, $p = 0.154$, and $p = 0.334$, respectively), atezolizumab (atezo) + bevacizumab (bev) ($p = 0.921$, $p = 0.566$, $p = 0.885$, and $p = 0.874$, respectively) or atezo monotherapy ($p = 0.332$ and $p = 0.165$, $p = 0.854$, and $p = 0.908$, respectively) arms. Median survival time per group is indicated. All p values are provided for descriptive purposes only, and were not adjusted for multiple comparisons. Sample number per group and time point indicated below graphs.

Supplementary Figure 7



Association between presence of *VHL* and *PBRM1* loss-of-function mutations and angiogenesis gene signature scores. Mean angiogenesis signature scores are higher in patients who are mutant for *VHL* (two-tailed *t* test, $p = 0.0003$) or *PBRM1* (two-tailed *t* test, $p = 3.88 \times 10^{-5}$) than in those who are non-mutant. Box plot elements are defined in the Methods section. Sample number per group indicated above each graph.

Supplementary Figure 8



Association between presence of *VHL* loss-of-function mutations and progression-free survival (PFS). Kaplan-Meier plots compare *VHL* mutant vs non-mutant patients in each treatment arm. Median survival time per group is indicated. Censored data are indicated by vertical tick marks. Hazard ratios (HRs), confidence intervals (CIs) and *p* values were calculated using Cox proportional hazards regression models (for details, see Methods section). *p* values reported are for descriptive purpose only and were not adjusted for multiple comparisons. Sample number per group and time point indicated below graphs. Atezo, atezolizumab, Bev, bevacizumab.

Supplementary Table 1. Demographic and baseline characteristics in ITT and biomarker evaluable populations. Sample numbers are given (percentage of total population indicated in parentheses).

Covariate		ITT (%)	RNAseq (%)	WES (%)
Male sex		230 (75)	201 (76)	154 (74)
Prior nephrectomy		265 (87)	233 (89)	189 (91)
Has liver metastasis		73 (24)	66 (25)	47 (23)
PD-L1+		172 (56)	157 (60)	128 (62)
MSKCC	Favorable	77 (25)	59 (22)	47 (23)
	Intermediate	201 (66)	181 (69)	148 (71)
	Poor	27 (9)	23 (9)	13 (6)
Fuhrman grade	Grade 1	5 (2)	5 (2)	4 (2)
	Grade 2	38 (12)	32 (12)	30 (14)
	Grade 3	80 (26)	72 (27)	54 (26)
	Grade 4	73 (24)	63 (24)	51 (25)
	N/A	109 (36)	91 (35)	69 (33)

ITT, intent-to-treat; MSKCC, Memorial Sloan Kettering Cancer Center; N/A, not available; PD-L1, programmed death-ligand 1; RNAseq, RNA sequencing; WES, whole exome sequencing.

Supplementary Table 2. Exploratory PFS HRs in biomarker subpopulations. HRs, 95% CIs (in parentheses) and *p* values calculated using Cox proportional hazards regression models (for details, see Methods section). Sample number (n) per group indicated in brackets.

	Across Arm Analysis			Within Arm Analysis		
PFS, HR (95% CI)	**Atezo + Bev vs Sunitinib**	**Atezo vs Sunitinib**	**Atezo + Bev vs Atezo**	**Atezo + Bev**	**Sunitinib**	**Atezo**
Subpopulation						
Angio^{High}	1.36 (0.78-2.36) *p* = 0.283 [n = 45;44]	1.46 (0.81-2.60) *p* = 0.206 [n = 43;44]	0.93 (0.54-1.60) *p* = 0.799 [n = 45;43]	**Angio^{High} vs Angio^{Low}**		
Angio^{Low}	0.59 (0.35-0.98) *p* = 0.042 [n = 43;45]	0.75 (0.45-1.25) *p* = 0.270 [n = 43;45]	0.78 (0.46-1.33) *p* = 0.359 [n = 43;43]	0.90 (0.54-1.51) *p* = 0.697 [n = 45;43]	0.31 (0.18-0.55) *p* < 0.001 [n = 44;45]	0.74 (0.42-1.28) *p* = 0.274 [n = 43;43]
Teff^{High}	0.55 (0.32-0.95) *p* = 0.033 [n = 43;43]	0.85 (0.50-1.43) *p* = 0.537 [n = 46;43]	0.65 (0.37-1.14) *p* = 0.130 [n = 43;46]	**Teff^{High} vs Teff^{Low}**		
Teff^{Low}	1.41 (0.85-2.36) *p* = 0.188 [n = 45;46]	1.33 (0.76-2.33) *p* = 0.319 [n = 40;46]	1.06 (0.63-1.79) *p* = 0.820 [n = 45;40]	0.50 (0.30-0.86) *p* = 0.011 [n = 43;45]	1.31 (0.77-2.23) *p* = 0.320 [n = 43;46]	0.83 (0.48-1.45) *p* = 0.516 [n = 46;40]
Myeloid^{High}	1.31 (0.79-2.17) *p* = 0.301 [n = 45,47]	2.03 (1.21-3.40) *p* = 0.007 [n = 40;47]	0.64 (0.39-1.06) *p* = 0.083 [n = 45;40]	**Myeloid^{High} vs Myeloid^{Low}**		
Myeloid^{Low}	0.57 (0.33-0.99) *p* = 0.047 [n = 43;42]	0.53 (0.30-0.96) *p* = 0.034 [n = 46;42]	1.07 (0.59-1.93) *p* = 0.822 [n = 43;46]	1.71 (1.01-2.88) *p* = 0.046 [n = 45;43]	0.82 (0.48-1.39) *p* = 0.452 [n = 47;42]	2.98 (1.68-5.29) *p* < 0.001 [n = 40;46]
Teff^{High}Myeloid^{High}	0.45 (0.20-1.05) *p* = 0.064 [n = 19;25]	1.81 (0.92-3.58) *p* = 0.086 [n = 22;25]	0.25 (0.10-0.60) *p* = 0.002 [n = 19;22]	**Teff^{High}Myeloid^{High} vs Teff^{High}Myeloid^{Low}**		
Teff^{High}Myeloid^{Low}	0.6 (0.28-1.31) *p* = 0.199 [n = 24;18]	0.47 (0.20-1.09) *p* = 0.077 [n = 24;18]	1.29 (0.57-2.90) *p* = 0.546 [n = 24;24]	0.80 (0.34-1.87) *p* = 0.604 [n = 19;24]	1.10 (0.53-2.29) *p* = 0.797 [n = 25;18]	3.82 (1.70-8.60) *p* = 0.001 [n = 22;24]
***VHL* mutant**	1.05 (0.59-1.85) *p* = 0.877 [n = 36;47]	1.25 (0.71-2.21) *p* = 0.438 [n = 45;47]	0.84 (0.45-1.50) *p* = 0.547 [n = 36;45]	***VHL* mutant vs *VHL* non-mutant**		
***VHL* non-mutant**	0.59 (0.31-1.16) *p* = 0.125 [n = 29;25]	1.08 (0.57-2.04) *p* = 0.822 [n = 26;25]	0.55 (0.29-1.05) *p* = 0.071 [n = 29;26]	1.02 (0.55-1.89) *p* = 0.951 [n = 36;29]	0.54 (0.29-1) *p* = 0.050 [n = 47;25]	0.67 (0.37-1.23) *p* = 0.196 [n = 45;26]
***PBRM1* mutant**	1.05 (0.53-2.11) *p* = 0.889 [n = 29;33]	2.49 (1.26-4.91) *p* = 0.008 [n = 30;33]	0.42 (0.22-0.82) *p* = 0.011 [n = 29;30]	***PBRM1* mutant vs *PBRM1* non-mutant**		
***PBRM1* non-mutant**	0.73 (0.42-1.27) *p* = 0.266 [n = 36;39]	0.73 (0.42-1.27) *p* = 0.262 [n = 41;39]	1.00 (0.56-1.78) *p* = 0.997 [n = 36;41]	0.67 (0.36-1.25) *p* = 0.205 [n = 29;36]	0.38 (0.20-0.73) *p* = 0.003 [n = 33;39]	1.33 (0.73-2.42) *p* = 0.358 [n = 30;41]

Angio, angiogenesis; Atezo, atezolizumab; Bev, bevacizumab; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; Teff, T effector.
p values are for descriptive purposes only.

Supplementary Table 3. Ad hoc analysis of IRF-assessed PFS by IMDC risk groups for atezolizumab + bevacizumab vs sunitinib.

	IMDC Score Category[a]		
	Low (0)	**Intermediate (1-2)**	**High (3+)**
Total, n	58	120	24
HR (95% CI)	0.79 (0.37-1.67)	1.10 (0.71-1.70)	0.78 (0.28 -2.16)

CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IRF, independent review facility; PFS, progression-free survival.

[a]IMDC risk group was derived ad hoc from baseline data collected in electronic care report form.